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09/653,730	09/01/2000	Marvin Whiteley	UIZ-038	5801

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EXAMINER
HINES, JANA A

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1645	9

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/653,730	Applicant(s) WHITELEY ET AL.	
	Examiner Ja-Na A Hines	Art Unit 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *27-74* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Claims 27-74 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected claims, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 8. Therefore, claims 1-26 of Group I are under consideration in this office action.

Specification

2. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

The disclosure is objected to because of the following informalities: The attempt to incorporate subject matter into this application by reference to websites on page 21 lines 33 and page 30 lines 12 and 26 is improper because Applicants have embedded a hyperlink which is impermissible and requires deletion. This attempt to incorporate subject matter into the patent by reference is improper because PTO policy does not permit the PTO to link to any commercial sites since the PTO exercises no control over those organizations, views or accuracy of the information contained on those outside sites. Appropriate correction is required.

3. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

4. The use of the trademark ABLAST™, ALGIN™ and GAP™ have been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying a modulator of quorum sensing signaling in bacteria wherein said method comprises: providing a cell which comprises a quorum sensing controlled gene wherein the cell comprises a reporter gene as a means for generating a detectable signal; a contact step; a detection step

wherein the amount of B-galactosidase activity is measured and the correlation of the measured amount of Beta-galactosidase detected is the detectable signal which would identify the test compound as a modulator of quorum sensing signaling in bacteria does not reasonably provide enablement for a method for identifying a modulator of quorum sensing signaling in bacteria wherein said method comprises: providing a cell which comprises a quorum sensing controlled gene wherein the cell comprises a quorum sensing controlled gene; contacting said cell with a quorum sensing signal molecule in the presence and absence of a test compound and detecting a change in the detectable signal to thereby identify said test compound as a modulator of quorum sensing signaling in bacteria. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The specification teaches at example 2, the screening assay for quorum sensing inhibiting compounds that cells were provided, incubating the cells and adding the test compounds to strains which expressed B-galactosidase only in response to the signal; and the inhibition of signaling was evaluated qualitatively by the absence or weakening of the blue color development. Example 1 teaches the use of plasmid that contains the *lacZ* reporter gene. Example 3 teaches the procedural overview of the assay wherein the reporter strain carries the reporter gene *lacZ* (page 48 line 24). Example 6 teaches using green fluorescent proteins as a means of detection (page 53 lines 1-25). Thus, the strains comprise a reporter gene that enables detection of a signal to occur.

There is no teaching within the specification of other means of detection without the use of a receptor gene. The specification fails to teach examples of other modes of detecting a change in the detectable signal when there is no requirement for any component within the method to comprise a reporter gene or some mode of detection. Therefore, the specification fails to enable a method for identifying a modulator of quorum sensing signaling in bacteria wherein said method comprises the recited steps.

Applicants' have provided no guidance to enable one of skill in the art to determine, without undue experimentation, a method for identifying a modulator of quorum sensing signaling in bacteria wherein said method recites that the detectable signal can be measured but does not require any detectable components within the method. If there are no detectable components associated with the cell, then one cannot detect a change; therefore the method is unpredictable, since there are no steps that teach what components are required to create a detectable change. One could not predict whether there would be a change to detect, if the method lacks detectable components.

Given the lack of guidance contained in the specification and the unpredictability for identifying a modulator of quorum sensing signaling in bacteria wherein there is no means of detection, one of skill in the art could not make or use the broadly claimed invention without undue experimentation. The specification fails to provide an enabling disclosure for a method for identifying a modulator of quorum sensing signaling in bacteria, simply comprising a provision step; a contact step and a detection step; when there are no requirements that the cell comprise a means for detection which could

meet the limitations of a method of identification as recited in the claims. In view of the lack of guidance contained in the specification and the unpredictability for identifying a modulator of quorum sensing signaling in bacteria, one skilled in the art could not make or use the broadly claimed invention without undue experimentation.

6. Claims 1-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is unclear. It is unclear whether the cell which comprises a quorum sensing controlled gene must posses a means, such as a reporter gene, to allow a detectable signal to be generated or if there is some other way to allow the generation of the detectable signal to occur. Thus, it is unclear whether a detectable signal will be generated. If the cell must comprise a reporter gene to allow a detectable signal to be generated then the cell must also comprise the reporter gene. Therefore, appropriate is required.

7. Claim 26 is unclear. It is unclear how to define a modulator that scavenges the quorum sensing signal molecule. Neither the specification nor the claims define "scavenges." Therefore, it is unclear how to define the phrase; as such the metes and bounds of the claim cannot be determined. Therefore, appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-7, 9-10, 13-15, 17-26 are rejected under 35 U.S.C. 102(b) as being anticipated by Pearson et al., (J. of Bacterio. 1997. 179(18): 5756-5767). Pearson et al., teach the roles of *Pseudomonas aeruginosa las* and *rhl* quorum-sensing systems in control of elastase and rhamnolipid biosynthesis genes. There are two quorum-sensing systems (*las* and *rhl*) that regulate virulence gene expression in *Pseudomonas aeruginosa* (abstract). It is well known in the art that rhl and las systems are involved in regulating the expression of a number of secreted virulence factors and biofilm development (see instant specification at page 12 lines 12-17 for additional references and/or Pesci et al., 1997). Quorum sensing involves the emission of an N-acyl homoserine lactone signal, an autoinducer generated by a Lux-I type autoinducer synthase (page 5756). A second quorum-sensing system is *rhl* that regulates the production of rhamnolipid that has both hemolytic and biosurfactant properties (page 5756). The quorum sensing signal molecules are *las* and *rhl*. The Materials and Method section teaches DNA techniques and the construction of *Pseudomonas aeruginosa lasI* and *lasR* mutants (page 5757). Bioassays for the rhl autoinducer were taught wherein the assay was developed in *E.coli* that contained the constructed plasmid carrying the mutation and a *lacZ* reporter gene wherein the presence or absence of B-galactosidase

activity was measured (page 5758). Thus, a wild type *E.coli* does not express the quorum sensing signal molecule. The *E.coli* cell comprises a quorum sensing controlled gene and is responsive to a quorum sensing signal molecule such that a detectable signal is generated. The cell comprises a reporter gene is lacZ which is controls B-galactosidase activity, which is the detectable change. In order to identify components of *Pseudomonas aeruginosa* that are necessary and sufficient for expression of the *rhlA* gene, the authors invented a bioassay for quorum sensing control in *E.coli* DH5α by cloning a plasmid that contained an rhlA'lacZ fusion and tacp-rhlR (page 5762). Quorum-sensing control of *rhlA* was shown to require *rhlR* and the production of rhamnolipids was shown to depend on *rhlR* and either *rhlI* or PAI-2, which modulated the quorum sensing (page 5762). The system was modulated and allowed the increased expression of *rhlA* by more than 300-fold, however in contrast, the compound PAI-1 has almost no effect on *rhlA* expression (page 5762). Therefore, the inventor concluded that PAI-2 is a modulator of quorum sensing signaling in bacteria (page 5762). Figure 4 shows a dose response wherein increasing amounts of PAI-2 increase expression of *rhlA* in the presence of RhlR, the quorum sensing molecule, and increasing concentrations of PAI-2, the test compound, was monitored with B-galactosidase activity assays. A control for LasR-mediated *lasB'-lacZ* expression was constructed (page 5763). It was found that high concentrations of PAI-1 caused both *lasB* expression and *rhlA* expression to decrease in *E.coli* expressing LasR, these negative effects appear similar to the results of *E.coli* expressing the *V.fischeri* LuxR wherein low levels of VAI-1 activated *luxR* expression and high levels of VAI-1

repressed expression (page 5764). Therefore, when PAI-1 decreased *rhlA* expression, there was an inhibition, which thereby inhibited the cells ability to regulate virulence gene expression, which is the equivalent of inhibiting the host defense mechanism, since the normally produces *rhl* which express components associated with the host defense mechanism.

Therefore, Pearson et al., teach a method for identifying a modulator of quorum sensing signaling in bacteria, said method comprising: providing a cell which comprises a quorum sensing controlled gene wherein the comprises a quorum sensing controlled gene; contacting said cell with a quorum sensing signal molecule in the presence and absence of a test compound and detecting a change in the detectable signal to thereby identify said test compound as a modulator of quorum sensing signaling in bacteria.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 8, 11,-12 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pearson et al., (J. of Bacterio. 1997. 179(18): 5756-5767) in view of Passador et al., (Science, 1993. 260:1127-1130). Pearson et al., have been discussed above, however Pearson et al., do not teach the method wherein the quorum sensing signal molecule is produced by a second cell.

Passador et al., teach expression of *P.aeruginosa* virulence genes requires cell-to-cell communication. The expression of elastase, one virulence factor produced by the organisms requires the transcriptional activator LasR (abstract). The role of elastase as a virulence factor is supported by the list of substrates that is uses, thus *lasA* and *lasB* appear to be global regulators of genes involved in the virulence of *P.aeruginosa* (page 1127-28). The *P.aeruginosa* strain PAO-RI, in which the lasR gene is inactivated, exhibits no detectable elastase activity or antigen, however the activity can be restored (page 1128). The experiments show that the *lasI* gene is involved in the synthesis of a diffusible molecule termed *P.aeruginosa* autoinducer (PAI) that provides a means of cell-to-cell communication that is required for the expression of virulence genes (abstract). In this system the expression of *lasB* is monitored by measuring B-galactosidase production from PAO-RI carrying the fusion in the presence of the *lasB::lacZ* or absence of the fusion plasmid (page 1129). The data indicates that LasI is involved in the production of a diffusible AI-like molecule termed PAI and that both LasR and PAI are required for maximum *lasB* expression (page 1130) which one cell produces, whereby the other cell can respond to the production of the molecule. The mechanism for cell-cell communication between *P.aeruginosa* cells or between *P.aeruginosa* and other bacterial cells allows the coordinate expression of virulence-associated genes when carried out under the proper environmental conditions (page 1130) whereby two cells communicate, one cell produces the signal molecule while the other cell responds to the molecule.

Therefore, it would have been prima facie obvious at the time of applicants invention to modify the method for identifying a modulator of quorum sensing signaling in bacteria comprising the recited steps as taught by Pearson et al., to include a second cell that produces the quorum sensing signal molecule, instead of adding the molecule to the cell. One would have a reasonable expectation of success in using a second cell to produce the molecule since Passador et al., teach that the expression of *P.aeruginosa* virulence genes requires cell-to-cell communication whereby one cell produces the molecule and the other cell can respond to the production of the molecule. Moreover, no more than routine skill would have been required to incorporate a second cell which is a wild type *P.aeruginosa* cell that express one of the virulence factors, using cells constructed in a similar manner as the cells of Pearson et al., which allows detection of a change to identify a compound as a modulator of quorum sensing signaling in bacteria.

Prior Art

10. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Latifi et al., (1996) teach the expression of *P.aeruginosa* virulence genes. Passador et al., (1996) teach functional analysis of the *P.aeruginosa* autoinducer PAI. Pearson et al., (1994) teach structure of the autoinducer required for expression of *P.aeruginosa* virulence genes. Pearson et al., (US Patent 5,59,872) teach autoinducer molecules that regulate gene expression in bacterium. Pesci et al., (1997) teach regulation of las and rhl quorum sensing in *P.aeruginosa*. Winson et al., teach

multiple N-acyl-L-homoserine lactone signal molecules regulate production of virulence determinants and secondary metabolites in *P.aeruginosa.*

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 703-305-0487. The examiner can normally be reached on Monday-Thursday and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 703-308-3909. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Ja-Na Hines
September 16, 2002

LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600